

This Week's Citation Classic

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Ross R & Glomset J A. The pathogenesis of atherosclerosis. *N*.

Engl. J. Med. 295:369-77; 420-5, 1976.

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The structure of the normal artery wall and data on our understanding of the cell biology of endothelium and smooth muscle *in vitro* and *in vivo* are covered. Three hypotheses of atherogenesis are discussed including the 'response to injury hypothesis,'¹ the 'monoclonal hypothesis,'² and the 'clonal senescence hypothesis.'³ These are each evaluated, compared, and contrasted, and the potential role of lipids and connective tissues in atherogenesis is discussed. [The *SCI*[®] indicates that these papers have been cited over 980 times in 652 publications since 1976.]

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"The two-part paper on the pathogenesis of atherosclerosis written by John Glomset and myself began as a result of a request from the *New England Journal of Medicine* to write a review on studies that I had been pursuing on wound healing and inflammation. By the time that request had been received, John and I had, for a number of years, been very much involved in studying a number of aspects of the biology of arterial smooth muscle and endothelium and had become very much interested in the problems of atherogenesis and the state of the field. We spent many hours talking about various ideas and decided if we could convince the *New England Journal of Medicine* to change their invitation from one dealing with a review of wound healing to one dealing with

atherosclerosis that we would tackle the problem of trying to put into perspective many of the ideas that we had tossed around over the preceding years, with a particular view to examining the question from the viewpoint of the cell biologist.

"One unique feature of the school of medicine at the University of Washington was the fact that at particular points in time at least three hypotheses of atherogenesis had been developed,¹⁻³ surprisingly, all emanating from the same department! Since all three of these hypotheses had generated a fair amount of interest, we decided that after discussing the cell biology of the problem, those notions and ideas should be related to the hypotheses at that particular state of their development, with, we must admit, some bias toward the 'response to injury hypothesis of atherosclerosis' that we had proposed to test.

"We have been fortunate to receive wide recognition for our work on the 'response to injury hypothesis.' More important, we hope that this paper served as a catalyst to help change directions in this field. Our ideas have changed quite a bit since this review was written in 1976 and although some of the notions have proved to be correct, a number of them have changed with the advent of new information concerning the biology of endothelium, smooth muscle, and, in particular, of the monocyte/macrophage and the platelet and their potential role in this entire process. Therefore, the 'response to injury hypothesis' today appears somewhat different from the one published in the cited paper and probably in another five years' time, the one that we would propose today would again appear different based on new information as it becomes available. I have recently published a paper in this field."⁴

1. Ross R & Glomset J A. Atherosclerosis and the arterial smooth muscle cell. *Science* 180:1332-9, 1973.

2. Benditt E P & Benditt J M. Evidence for a monoclonal origin of human atherosclerotic plaques. *Proc. Nat. Acad. Sci. US* 70:1753-6, 1973.

3. Martin G, Ogburn C & Sprague C. Senescence and vascular disease. (Cristafalo V J, Roberts J & Adelman R C. eds.) *Exploration in aging*. New York: Plenum Press. 1975. p. 163-93.

4. Ross R. George Lyman Duff Memorial Lecture. Atherosclerosis—a problem of the biology of arterial wall cells and their interaction with blood components. *Arteriosclerosis* 1:293-311, 1981.